EXHIBIT Q

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Investigating Mesh Erosion in Pelvic Floor Repair

Report

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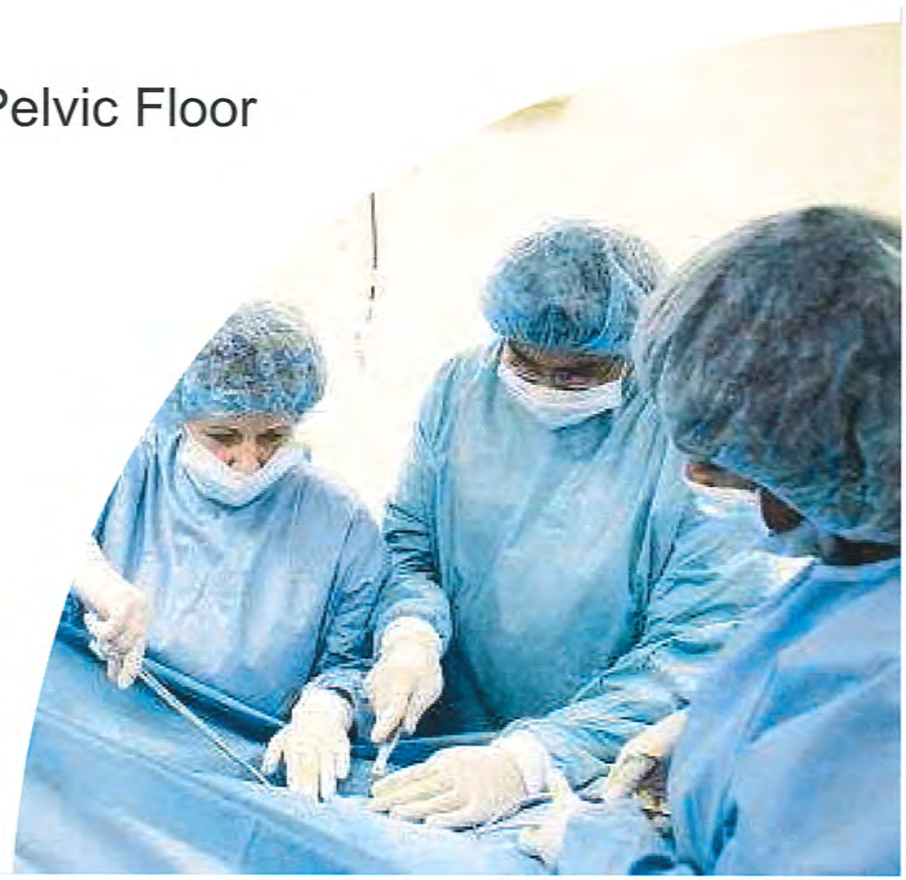
FPM-11-0024-R_C

CONFIDENTIAL between PA and J&J



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Mesh erosion in pelvic floor repair is a complication affecting 0 -20% of patients

- Johnson and Johnson Medical provide knitted meshes for use in pelvic floor repair surgical procedures
- A review of a substantive body of clinical studies report that 0-20% of pelvic floor repair procedures suffer post surgical complications of 'mesh erosion'; a condition in which the mesh migrates from its original location, ultimately resulting in exposure of the mesh
  - This can be associated with pain, irritation and infection
- J&J have investigated this issue - including an extensive literature search - to evaluate the causes of mesh erosion and hence to identify potential approaches to eliminating or reducing the incidence
- However, it has proved difficult to generate a clear answer as there are many variables which potentially affect the incidence of mesh erosion
  - Also, there is a lack of consistency in reporting clinical studies, which makes it difficult to make direct comparisons among different studies
    - There are for example, differences in procedures, products used, populations and clinical end point definitions
- J&J asked PA to review its existing literature research (Clinical Evaluation Report: Mesh Erosions; P. Meier, 13 September 2010) and to conduct a broad analysis of the problem of mesh erosion to include :
  - Surgeon and opinion leader interviews
  - A review of animal models
  - An informal meta-analysis of the literature

Mesh erosion can cause exposure of the mesh

Work programme to investigate mesh erosion

	1 Analyse the J&J literature search	2 Interview internal and external experts	3 Develop concepts for models for mesh erosion	4 Existing devices	5 Develop device concepts

Activities	▪ Kick-off project, introduce project teams
	▪ Analyse the literature search undertaken by J&J to identify causes of mesh erosion
		▪ Interview internal J&J personnel who have knowledge of mesh erosion
		▪ Interview external experts (clinicians)
		  ▪ Causes, effects, triggers, clinical disposition, predictive factors, trends
		  ▪ Competing procedures / products
		  ▪ Discuss animal models
			▪ Literature search for possible animal models
			▪ Using information obtained from interviews develop initial concepts for animal models (these will be concepts to explore, not working / functional models
				▪ Search for existing pelvic floor repair devices
				▪ Evaluate existing devices using
				  ▪ The literature
				  ▪ Interviews with practitioners
				  ▪ Interviews with J&J
				▪ Analyse mesh structure and materials using microscopy
					▪ Structured workshops and evaluation sessions to:
					  ▪ Develop concepts to reduce mesh erosion
					  - materials
					  - weave, structure
					  - drug eluting
					  - coatings
					  - new procedure
					  ▪ Evaluate concepts
					  ▪ Select concepts and develop them

Potential Outputs	▪ Root cause analysis of mesh erosion from the literature	▪ An analysis of the cause and effect of erosion caused by the mesh to complement the literature search ▪ Potential models	▪ Concepts for models for mesh erosion	▪ Understanding of opportunities for alternative mesh products which suffer less erosion ▪ Images of the mesh	▪ Selected product concepts, described as storyboards

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We have interviewed / met internal and external experts

Name	Specialism
Professor Klosterhalfern	Pathologist specialising in mesh failures
Rhona Kearney	Surgeon specialising in pelvic floor repair
Fiona Fynes	Surgeon specialising in pelvic floor repair
Mark Slack	Surgeon specialising in pelvic floor repair
Huntingdon Life Sciences	
Joerg Holste	Pre-clinical
Sandy Savage	Pre-clinical
Tim Muench	Pre-clinical
Susan Cooper	Textiles
Patrick Endoler	Sales
Peter Meier	R&D
Christoph Vaihe	R&D
Michael Richter	R&D

The Ethicon family of meshes for pelvic floor repair

PROLENE (polypropylene) mesh

Gynemesh PS

- PROLENE Soft: different knit to give 50% more flexibility

Ultrapro

- Partially absorbable mesh (equal parts of MONOCRYL and PROLENE)
- Also called Gynemesh M when used in PROLIFT+M system

TVT mesh

- Partially absorbable mesh (a sandwich structure consisting PROLENE, VICRYL and PDS)

GYNECARE® Family of Products for Pelvic Floor Repair	Products	Mesh	Mesh material	Other
1	**GYNEMESH® PS Nonabsorbable PROLENE® Soft Mesh**		knitted filament of extruded polypropylene. The mesh is constructed of reduced-diameter monofilament fibers, knitted into a unique design that results in a mesh that is approximately 50 percent more flexible than standard PROLENE™ Polypropylene Mesh	
2	**PROSIMA™ Pelvic Floor Repair System**	GYNEMESH® PS Nonabsorbable PROLENE® Soft Mesh	knitted filament of extruded polypropylene.	to treat symptomatic moderate pelvic organ prolapse
3	**PROLIFT® Pelvic Floor Repair System**	GYNEMESH* PS Nonabsorbable PROLENE* Soft Mesh	knitted filament of extruded polypropylene.	to treat symptomatic prolapse
4	**PROLIFT+M™ Pelvic Floor Repair System**	GYNEMESH M™ partially absorbable mesh	equal parts of absorbable poliglecaprone-25 (MONOCRYL) monofilament fiber and non-absorbable polypropylene monofilament fiber	

The Ethicon family of meshes for pelvic floor repair

GYNECARE TVT™(Tension-free Vaginal Tape) Family of Products for SUI (Stress Urinary Incontinence)	Products	Mesh	Mesh material	Other
1	**Gynecare TVT EXACT**	PROLENE™ Polypropylene Mesh.	PROLENE Mesh is constructed of knitted filaments of extruded polypropylene strands identical in composition to that used in PROLENE™ Polypropylene Nonabsorbable Surgical Sutures	Enhanced control
2	**Gynecare TVT ABBREVO**	PROLENE™ Polypropylene Mesh		Less mesh
3	**Gynecare TVT Retropubic system**	PROLENE™ Polypropylene Mesh		Gold standard
4	**Gynecare TVT Obturator system**	PROLENE™ Polypropylene Mesh		
5	**GYNECARE TVT SECUR™ System**	GYNECARE TVT™ mesh²	consisting of one piece of PROLENE* polypropylene mesh (tape) with pieces of fleece made from VICRYL* (polyglactin 910) and PDS*(poly-p-dioxanone) undyed yarn which sandwich the end sections of the mesh. The sandwich is bonded together in a thermal process using two pieces of dyed poly-p-dioxanone film	

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Mesh erosion is complex and the clinical studies do not give a clear picture, due to the diversity of variables

- The causes of mesh erosion are not well understood and may be triggered by mechanical tissue damage and/or by immunological rejection processes
  - Can occur along suture lines, mesh fold lines, rough edges
  - Can cause migration and bunching-up of the mesh
- There are many studies reporting the incidence of mesh-related infections; and erosion figures vary widely depending on the reporting author and the study
- Non-specific pelvic pain, persistent vaginal discharge or bleeding, dyspareunia, and urinary or fecal incontinence are the most common manifestations of vaginal mesh-related infection
- A variety of factors have the potential to influence the development of mesh-related complications; such as the type of polymeric material, mesh design and construction, the type of procedure and surgeon experience; together with patient characteristics and underlying comorbidity of the women treated
- The clinical literature[1] on mesh erosion paints a complex picture because of the diversity of studies conducted, the lack of commonality and number of variables which influence erosion
  - There are also potentially a number of issues observed clinically, which are

1 Ref J&J literature search; Clinical Evaluation Report Mesh Erosions, Peter Meier September 2010

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Mesh erosion is difficult to model *in vitro* or in pre-clinical studies; and it is difficult to study the clinical effect of product changes

- Product development efforts are complicated by the lack of a definitive animal model for *in-vivo* design validation
  - There are a number of physical mesh properties that may be varied, characterized and measured *in-vitro* but these cannot be easily related to observable outcomes
  - However, we note the general trend over time by all manufacturers to produce meshes with particular general characteristics i.e. larger pore size, monofilament construction, light weight, etc
- The situation with animal models is confusing; whilst there are claims in the literature for successful animal models as a predictor of product behaviour and performance, these have not been reproduced when adopted by J&J
- The clinically reported erosion rates are generally low (reported as zero in some studies) but cover a wide range (more than 20% in other studies) and take a significant time (months) to appear clinically
  - Hence pre-clinical studies would require a large number of animal subjects and an extended study period of many months
  - Product improvements are not easy to demonstrate in clinical studies without large comparative or retrospective trials

Mesh erosion is lower with PP meshes used in trans-abdominal surgery than in trans-vaginal surgery

- PA conducted an informal meta-analysis of the literature search supplied by J&J and supplemented this with additional literature searching
  - Despite the complexity of the area there are some indicators in the literature search conducted by J&J[1] and supported by the literature review undertaken by NICE[2]

Implants placed via the abdominal route suffer lower rates of mesh erosion than those placed during vaginal surgery and may show lower infection rates*

Polyester and PTFE meshes[3] suffer higher rates of erosion than polypropylene

*intuitively trans-vaginal surgery would be expected to show higher infection rates and this was confirmed by the surgeons interviewed and reporting authors

However the literature contains one paper which reports high infection rates for trans-abdominal surgery and this skews the data

1 Ref J&J literature search; Clinical Evaluation Report Mesh Erosions, Peter Meier September 2010

2 Systematic review of the efficacy and safety of using mesh or grafts in surgery for uterine or vaginal vault prolapse, Jia & Glazener et al

3 PTFE 'mesh' reported does not comprise a knitted structure, rather than a perforated membrane

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Surgeon skill may be an important factor in the risk of mesh erosion

- Interviews with practising surgeons suggests that surgeon skill could be a factor in the risk of mesh erosion occurring
- Leading UK gynaecologists who sub-specialise in vaginal floor repair tend to be conservative in their use of mesh, using it in limited cases (often only for revisions)
  - If they do use mesh, they tend to reject the trans-vaginal kits with the trocars and operate trans-abdominally, cutting out a piece of mesh to size and shape
  - None of those interviewed had problems with mesh erosion, although they had observed it
- The interviewees speculated that a significant contributor to observed erosion rates is insufficiently skilled surgeons using the trans-vaginal kits and essentially inserting the trocars "blind"
  - They maintain that mesh is sometimes used in cases where it is not necessary by an enthusiastic but less skilled general gynaecological surgeon
- Interviews also revealed that mesh failure within a few weeks of the operation may be more likely due to inappropriate deployment or placement of the mesh, rather than true erosion
  - It is possible to cause a minor perforation during surgery which can trigger infection
  - There is general agreement that once implanted, factors such as; folds or creases in the mesh, prominent suture lines, hard or rough edges all have a propensity to cause mesh erosion

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There are many variable factors which have potential to influence mesh erosion

- Materials and method of production define the mesh attributes and characteristics. These in turn influence the behaviour of the mesh once implanted. Mesh variables include:
  - Pore size – macro vs. micro
  - Filament construction; multifilament vs. monofilament
  - Mesh density (weight / unit area)
  - Pore depth
  - Surface area
  - Rigidity (resulting from filament gauge used and construction)
  - Elasticity
  - Filament surface effects, character, composition, extractables
- There are other variables which can impact on mesh behaviour, including
  - Surgical technique and approach
  - Surgical procedure
  - Patient characteristics and co-morbidities
  - Individual response

These are depicted on the diagram over page. The diagram is not intended to be exhaustive, but indicative of the level of complexity

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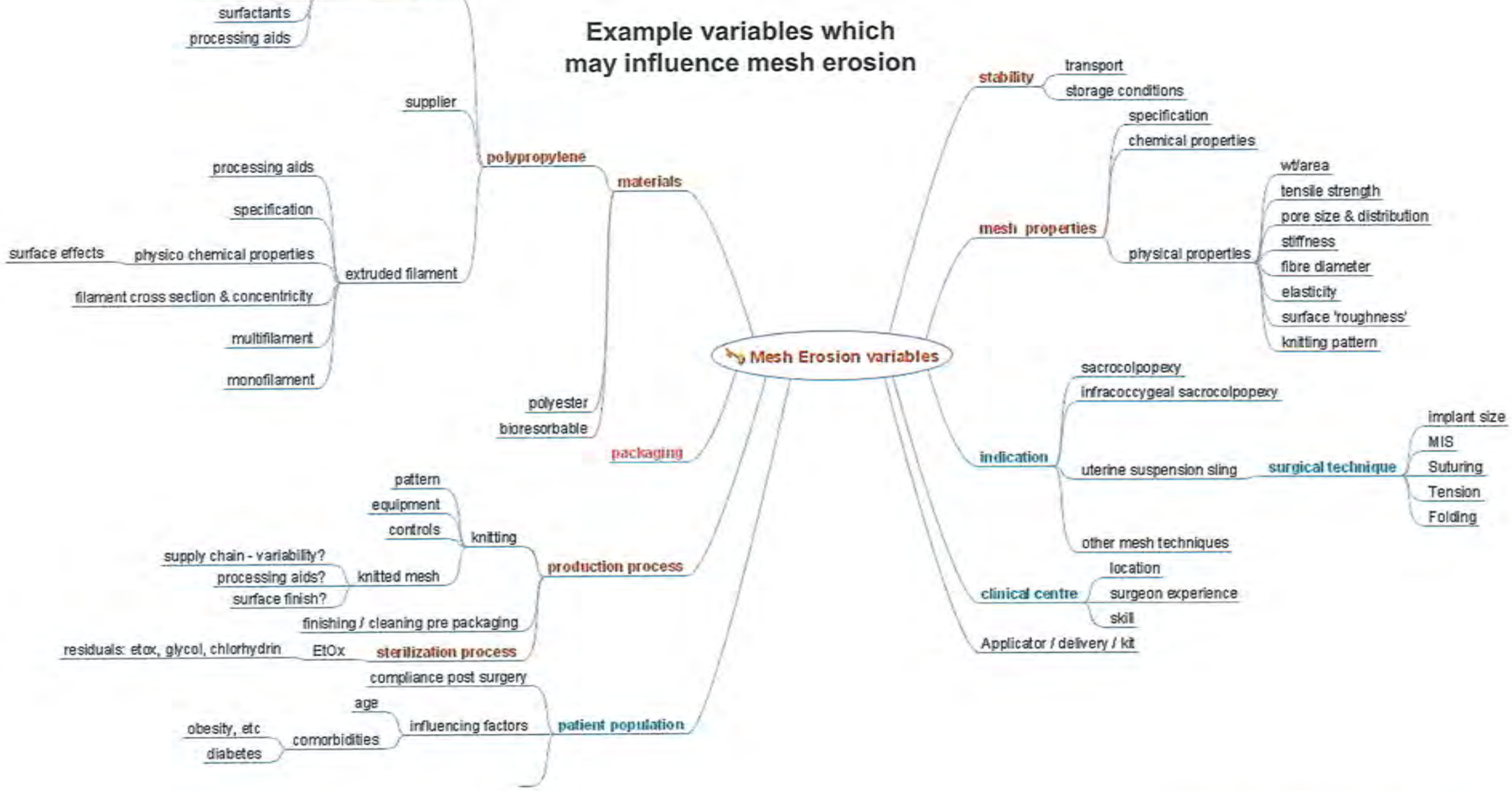
There are many variable factors which have potential to influence mesh erosion

Variables in red are in J&J's direct control, those in blue are not directly under control



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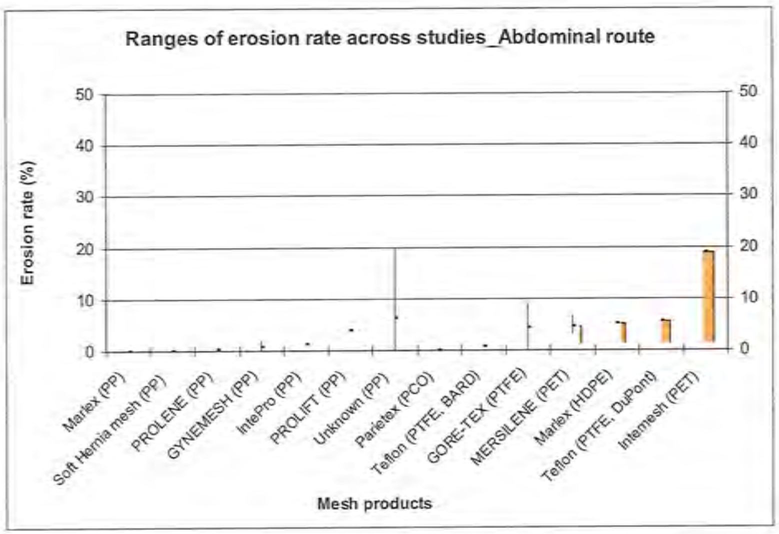
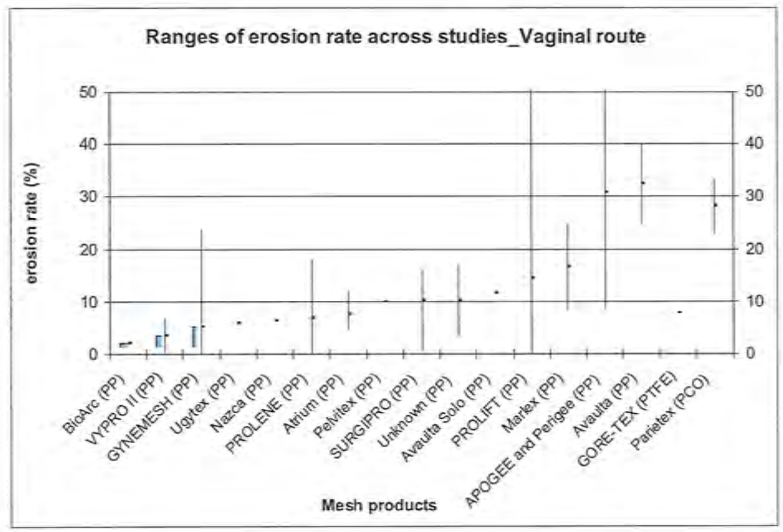
Vaginal surgery has a higher risk of mesh erosion than abdominal surgery

Analysis of erosion rate across the body literature by vaginal and abdominal surgery by brand of mesh used (all procedures, all study types, all patient numbers and groups, all follow up types where PA had the data available)





A high level meta-analysis of the data in the J&J literature search[1] was conducted and erosion rates from all studies therein were tabulated. Trans-vaginal implantation appears to show higher erosion rates than trans-abdominal surgery

1 Ref J&J literature search; Clinical Evaluation Report Mesh Erosions, Peter Meier September 2010

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Supporting data (all time periods)

Abdominal route

Summary	Product		Mean	Max	Min	Mean
1	Marlex (PP)	crystalline polypropylene	0	0.0	0.0	0.0
2	Soft Hernia mesh (PP)	PP	0	0.0	0.0	0.0
3	PROLENE (PP)	PP	0.3	0.8	0.0	0.3
4	GYNEMESH (PP)	PP	0.8	1.9	0.0	0.8
5	IntePro (PP)	PP	1.2	1.2	1.2	1.2
6	PROLIFT (PP)	PP	4	4.0	4.0	4.0
7	Unknown (PP)	PP	6.4	20.0	0.0	6.4
9	Parietex (PCO)	collagen coated polyester	0	0.0	0.0	0.0
10	Teflon (PTFE, BARD)	polytetrafluoroethylene	0.7	0.7	0.7	0.7
11	GORE-TEX (PTFE)	polytetrafluoroethylene	4.4	9.0	0.0	4.4
12	MERSILENE (PET)	Polyethylene terephthalate	4.7	6.9	3.1	4.7
13	Marlex (HDPE)	high-density polyethylene	5	5.0	5.0	5.0
14	Teflon (PTFE, DuPont)	polytetrafluoroethylene	5.5	5.5	5.5	5.5
15	Intemesh (PET)	silicone coated polyester	19	19.0	19.0	19.0

Vaginal route

Summary	Product		Mean	Max	Min	Mean
1	BioArc (PP)	PP	2.1	2.1	2.1	2.1
2	VYPRO II (PP)	PP	3.5	6.9	0	3.5
3	GYNEMESH (PP)	PP	5.2	24.0	0.0	5.2
4	Ugytex (PP)	PP	5.9	6.0	5.7	5.9
5	Nazca (PP)	PP	6.3	6.3	6.3	6.3
6	PROLENE (PP)	PP	6.9	18.0	0.0	6.9
7	Atrium (PP)	PP	7.5	12.0	4.7	7.5
8	Pelvitex (PP)	PP	10.0	10.0	10.0	10.0
9	SURGIPRO (PP)	PP	10.1	16.0	0.8	10.1
10	Unknown (PP)	PP	10.3	17.0	3.6	10.3
11	Avaulta Solo (PP)	PP	11.7	11.7	11.7	11.7
12	PROLIFT (PP)	PP	14.4	53.0	0.0	14.4
13	Marlex (PP)	crystalline polypropylene	16.7	25.0	8.4	16.7
14	APOGEE and Perigee (PP)	PP	30.8	53.0	8.6	30.8
15	Avaulta (PP)	collagen coated PP	32.5	40.0	25.0	32.5
16	GORE-TEX (PTFE)	polytetrafluoroethylene	7.8	7.8	7.8	7.8
17	Parietex (PCO)	collagen coated polyester	28.2	33.3	23.0	28.2

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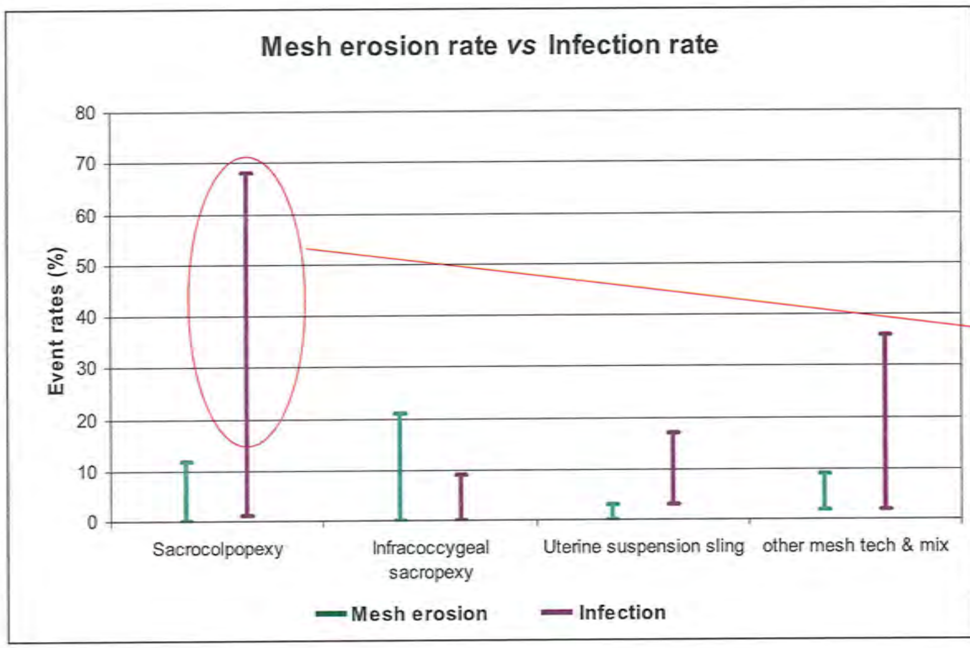
The Glazner[1] review also shows that trans vaginal surgery is more likely to lead to erosion than abdominal surgery although infection rates are higher



1. 'Systematic review of the efficacy and safety of using mesh or grafts in surgery for uterine or vaginal vault prolapse, Jia and Glazener, 2008.

The infection rates show more infections in trans-abdominal than trans-vaginal surgery, which is counter intuitive.

Of n=17, one paper using Gore-Tex trans-abdominally (68% infection rate, 52% of these minor pyrexia) by NG et al Singapore Medical J 2004: 45 475-81 is the only one which showed statistically significant differences in infection rates between mesh and non-mesh use. This is skewing the data overall

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The Glazner review also shows that trans vaginal surgery is more likely to lead to erosion than abdominal surgery although infection rates are higher (continued)

mesh techniques	surgical route	mesh erosion rate (%)	infection rate (%)
Sacrocolpopexy	A	0–12	1–68
Infracoccygeal sacropexy	B	0–21	0–9
Uterine suspension sling	A+B	0–3	3–17
other mesh tech & mix	A+B	2–9	2–36

A: abdomial route
B: vaginal route

	Sacrocolpopexy (%)	Infracoccygeal sacropexy (%)
Objective failure rate (clinical end point)	0 - 6	0 - 25
Subjective failure rate (patient self assessment)	3.3 - 31	2.3 - 21

It is not possible to compare efficacy and safety between different procedures or between different types of mesh for the same procedure, because few studies use the same comparator

The numbers of patients lost to follow up is also highly variable, reaching as high as 55%

1 Systematic review of the efficacy and safety of using mesh or grafts in surgery for uterine or vaginal vault prolapse, Jia & Glazener et al

It is counter intuitive that infection rates should be higher in trans-abdominal surgery than trans-vaginal surgery

- Inserted transvaginally, mesh traverses the vaginal area that caries many bacteria, hence, without protection, it is virtually impossible to insert mesh devices with out contamination
- Host cells and bacteria compete for dominance over the mesh surface, if the latter prevail the mesh is irreversibly contaminated and the bacteria may remain dormant for long periods, with the possibility of establishing a tissue infection later
- Mesh surface area may thus be significant in infection rates as it provides a greater potential for bacterial attachment
- Following insertion, there is a 'race for the surface' of the mesh between host cells and bacteria[1]. If the bacteria colonize the surface, they protect themselves with a bio film, preventing host defences from eliminating them
  - The graft is irreversibly contaminated and the bacteria may remain quiescent for long periods of time
  - Surface area is thus important owing to the large area available for potential bacterial attachment
- Pore size is significant[2]
  - >75micron allows for greater tissue in-growth
  - <10 microns interfere with host defences and discourages small blood vessel in-growth
  - WBC are 9-15x bigger than bacteria, hence the latter can invade spaces not accessible to the former

1. Gristina AG, Biomaterial centred infection: microbial adhesion vs. tissue integration. Science 1987; 237:1588-95
2. White RA, et al, Histopathologic observations after short term implantation of two porous elastomers in dogs. Biomaterials 1981; 2:171-6

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PA concludes that trans abdominal surgery has lower complication rates than trans-vaginal surgery

- Mesh erosion rate and infection rate vary depending on surgical techniques
- Trans-abdominal surgery (Sacrocolpopexy), exhibits a lower mesh erosion rate (0-12%) compared to trans-vaginal surgery (Infracoccygeal Sacropexy (0-21%)
- One paper reports 68% infection rate in sacrocolpopexy which is skewing the data
- There is no correlation between mesh erosion and surgical infection, although it is thought that there could be some misdiagnosis

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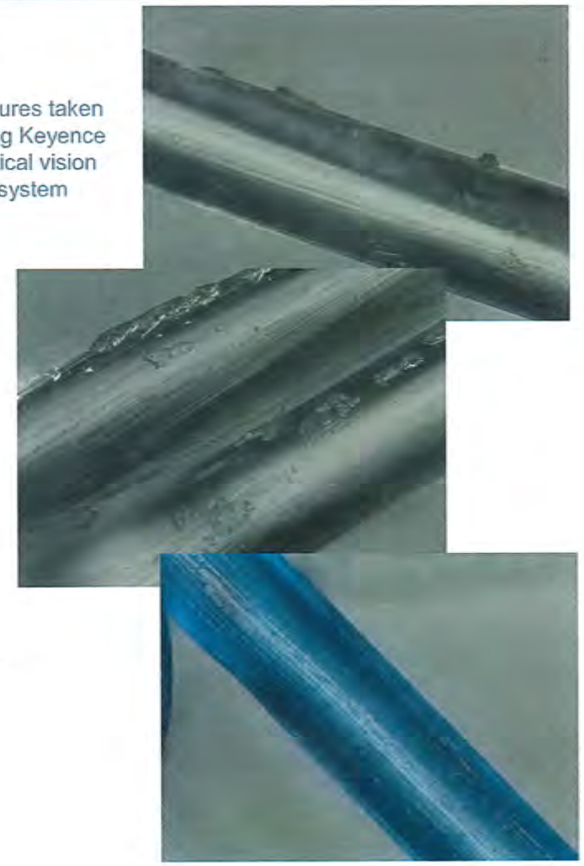
Mesh production processes could influence erosion risk

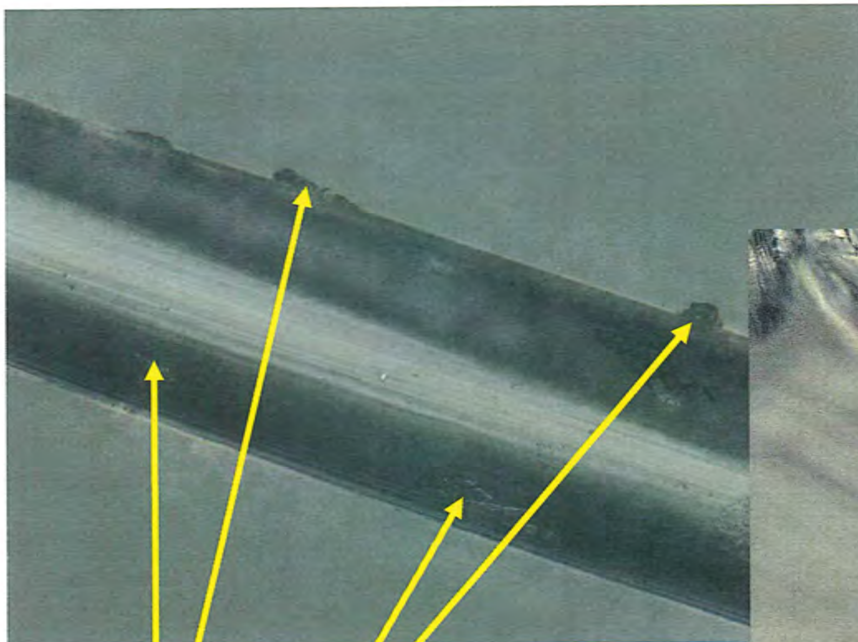
- There are many steps in the end-to-end production process, including:
  - Extrusion of continuous filament:
  - Winding
  - Knitting
  - Scouring
  - Annealing
  - Application of bio-resorbable layer for combination products
- PA was not able to review the production process as part of this assignment. Nor have we examined samples of materials at each stage of production
- However:
  - High magnification pictures of filaments within a random sample of finished products show a number of surface effects (note also images on the following slides)
  - It is not certain where in the production process these artefacts are generated; perhaps extrusion/winding and scouring
  - We cannot discount the possibility that this type of artefact contributes to the potential for undesirable clinical outcomes
  - There may be other variables in the process that also produce variations in the finished product that in turn, might influence the behaviour of the implanted mesh e.g. heat sealing

Pictures taken using Keyence optical vision system



Gynemesh PS

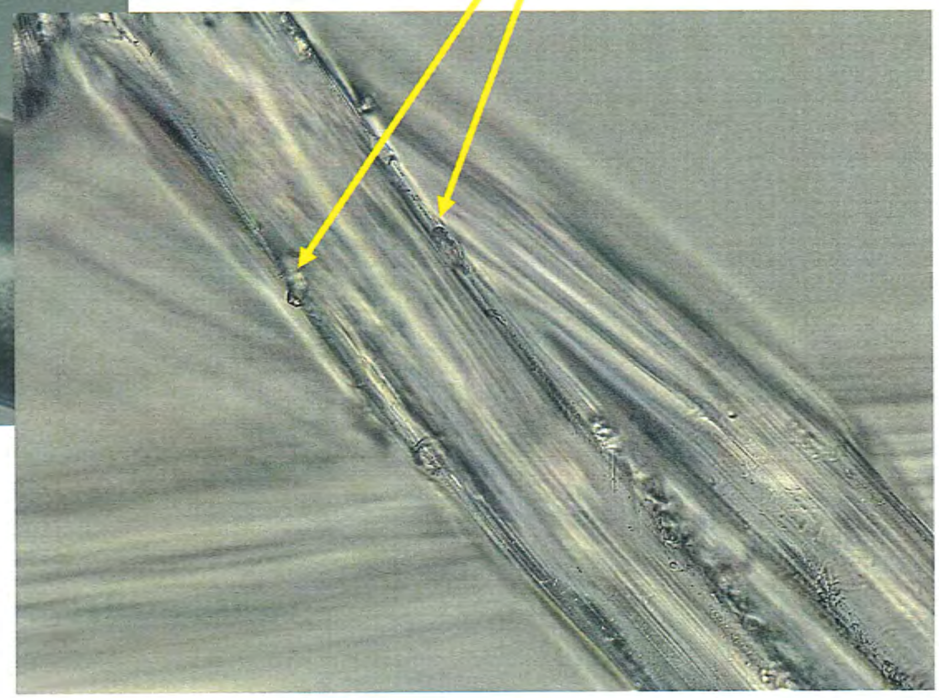
Gynemesh PS filaments exhibit artefacts on the surface



Artefacts on the filament surface

Lot # CR626,
Exp 2011-01

Artefacts on the filament surface



Pictures taken using Keyence optical vision system

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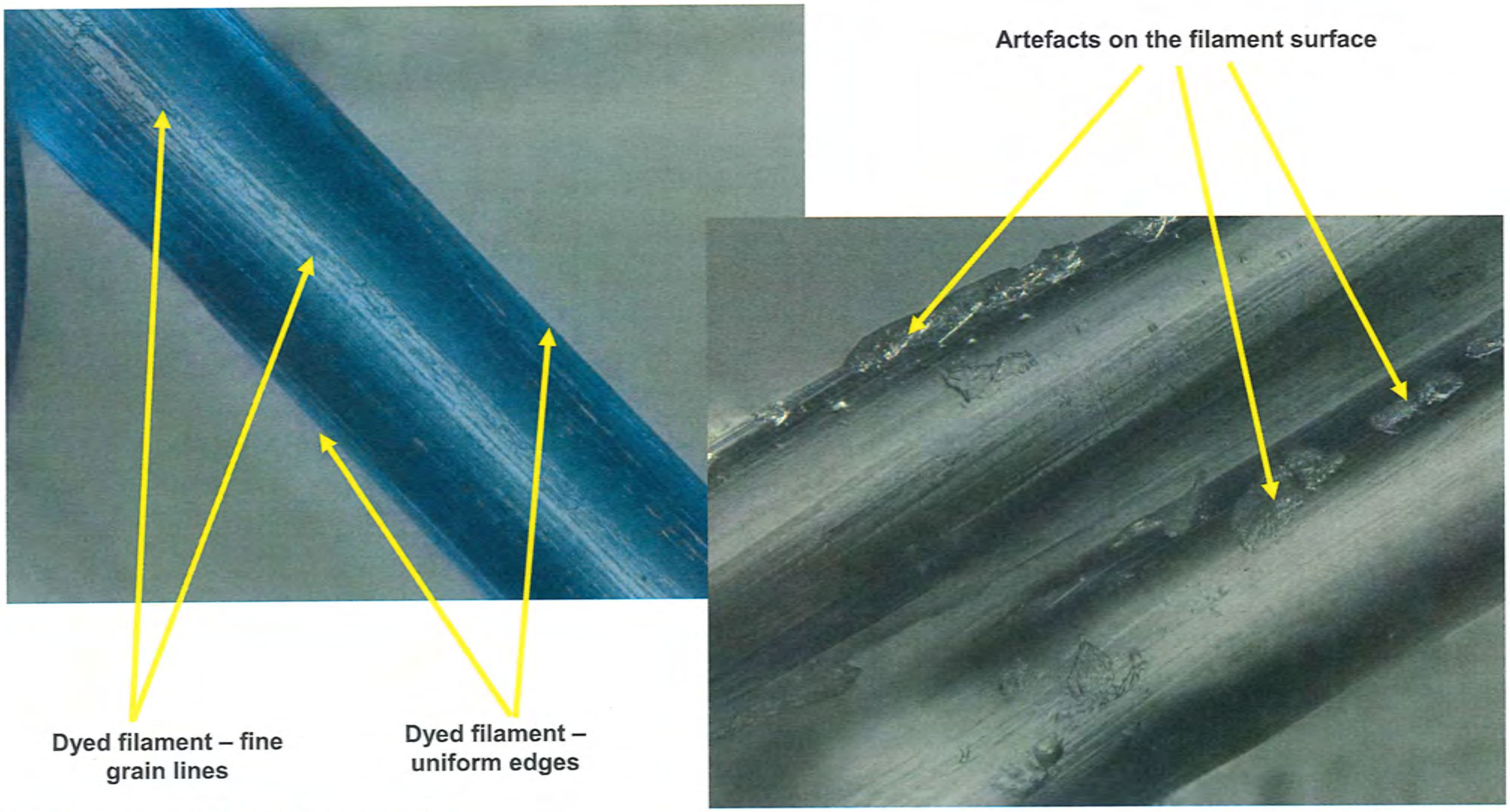
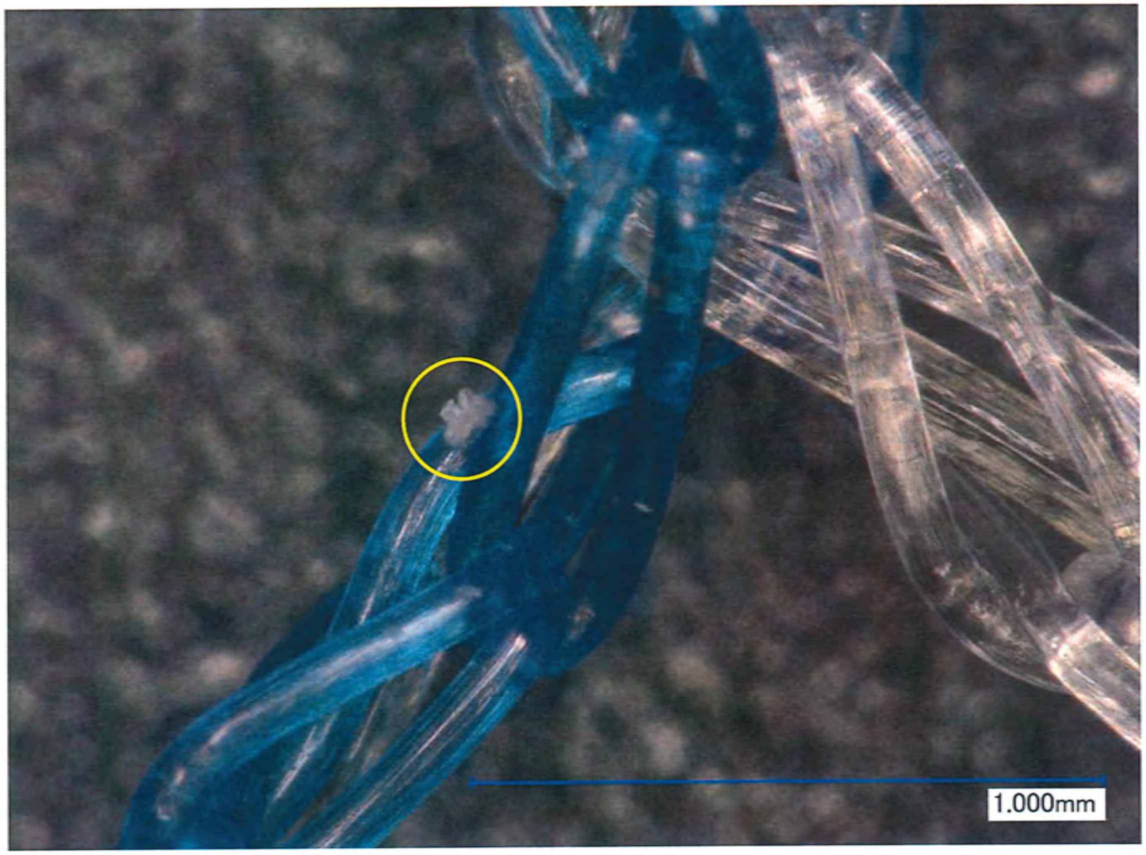
Gynemesh PS filaments exhibit artefacts on the surface (continued)



Pictures taken using Keyence optical vision system

Prolift +M filaments exhibit artefacts on the surface



Gynemesh M (Ultrapro)

Lot# BH8HCSZ0

Exp 2012-07

Pictures taken using Keyence optical vision system

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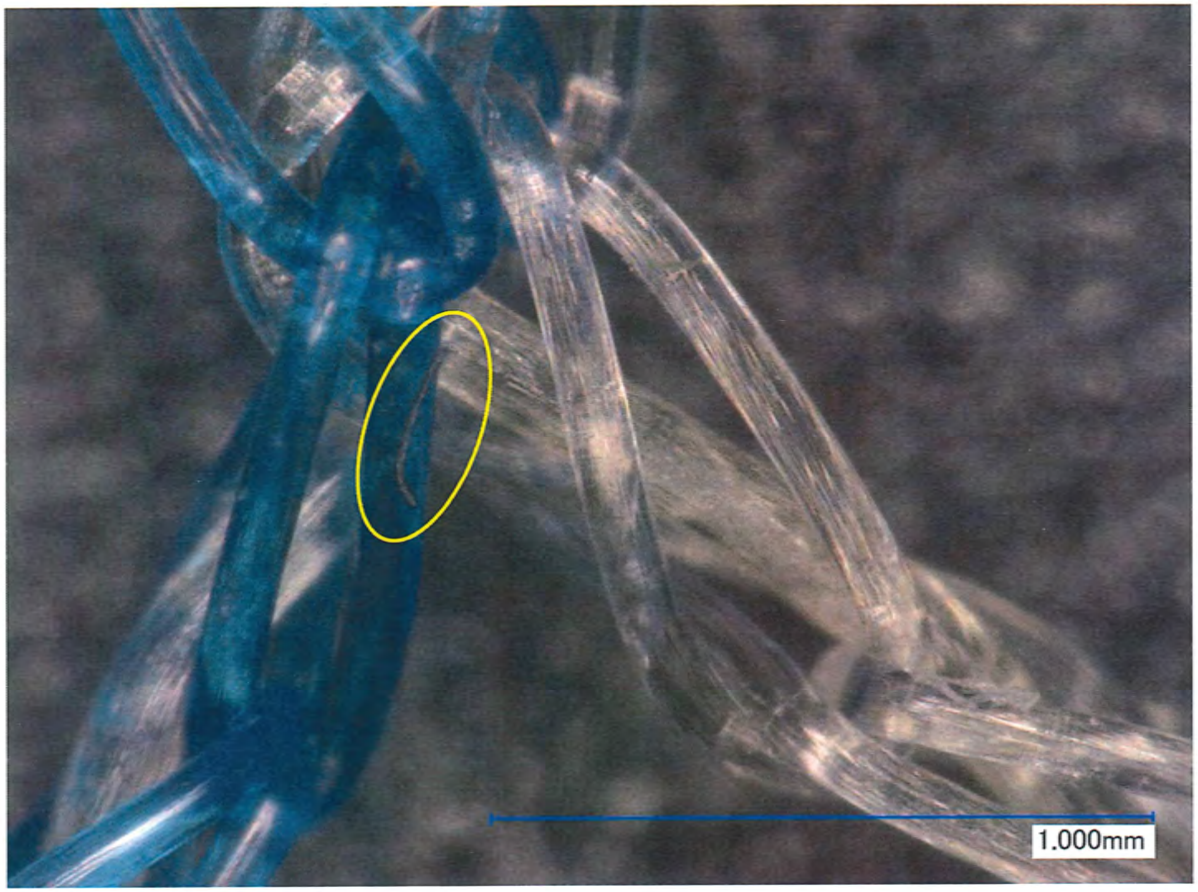
Prolift +M filaments exhibit artefacts on the surface (continued)



Pictures taken using Keyence optical vision system

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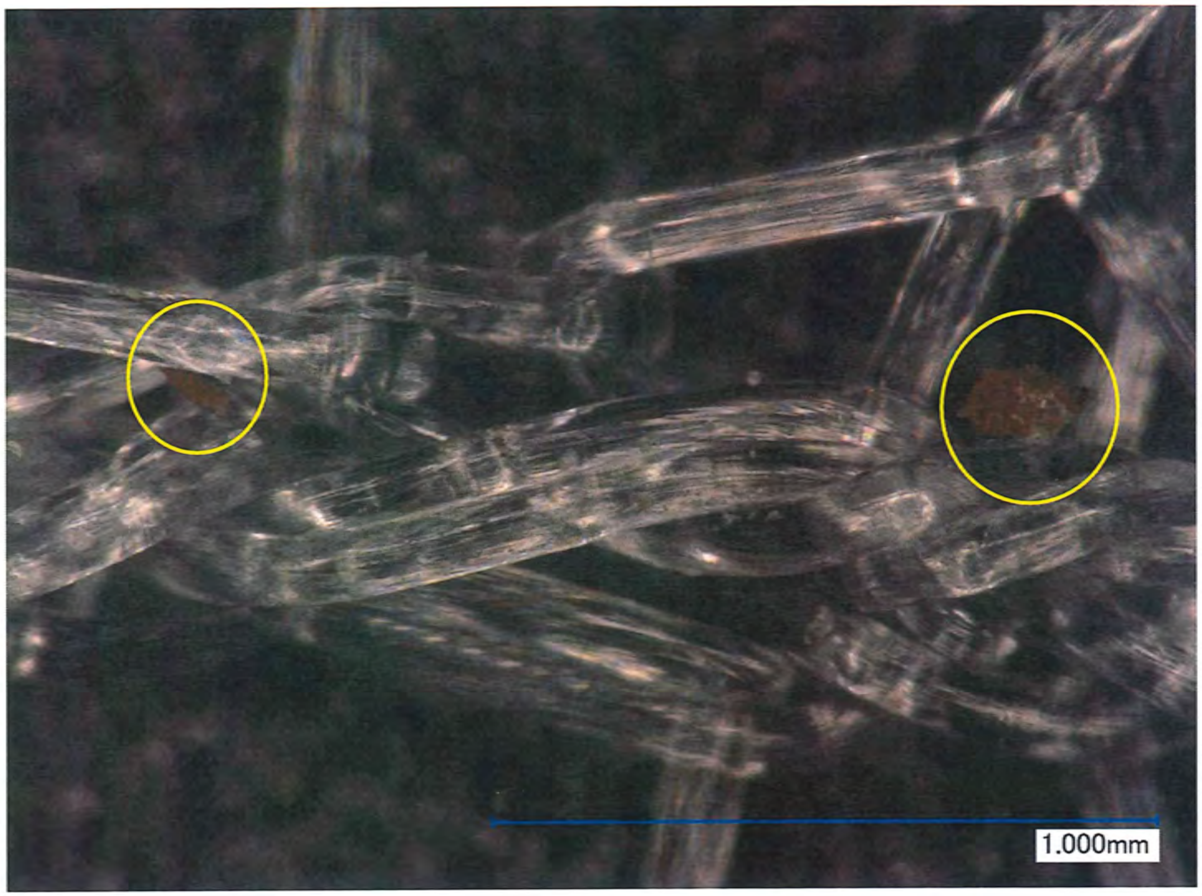
Prolift +M filaments exhibit artefacts on the surface (continued)

Pictures taken using Keyence optical vision system

Prosima filaments exhibit artefacts on the surface



(Gynemesh PS)

Lot# 3453224

Exp 2013-05

Note: the lot number refers to the entire kit.

The pouch containing the mesh within the kit is entirely blank, with no identifying labelling or numbering

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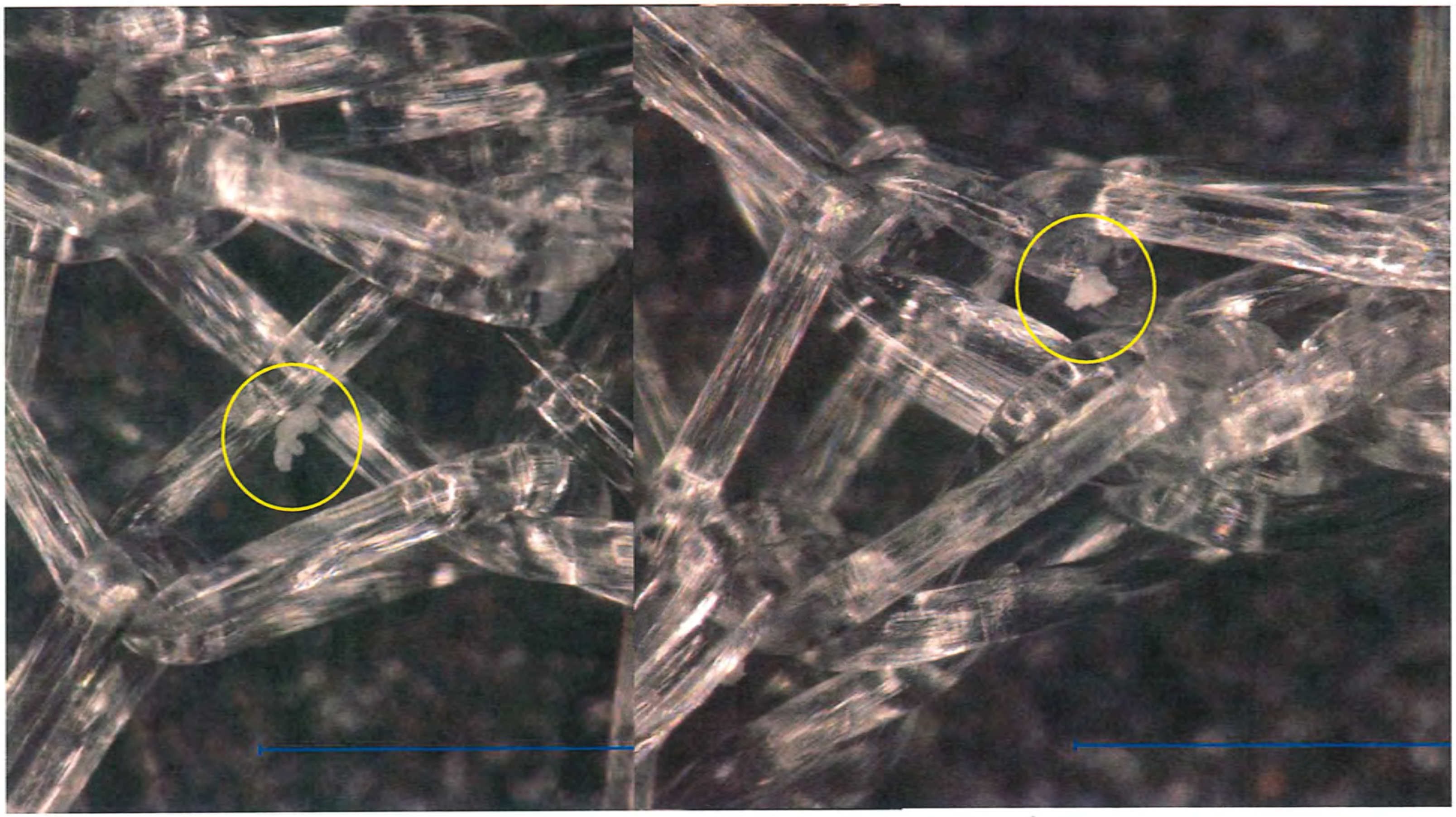
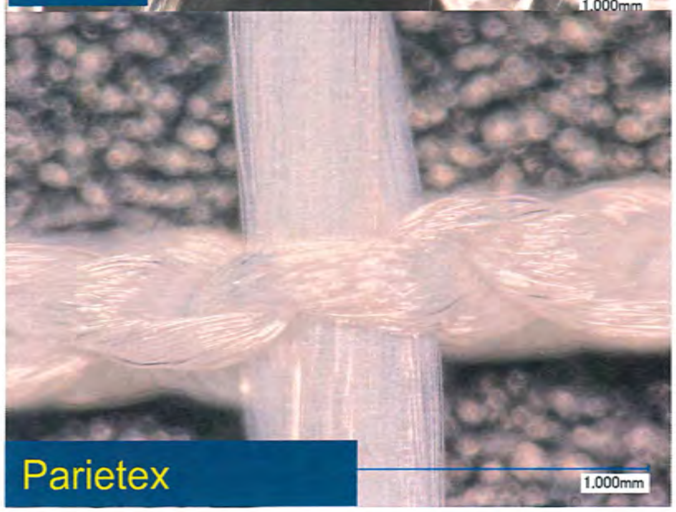
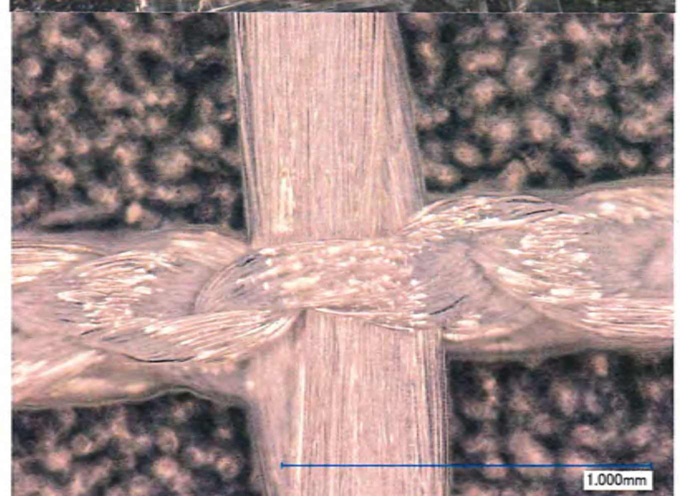
Prosima filaments exhibit artefacts on the surface (continued)



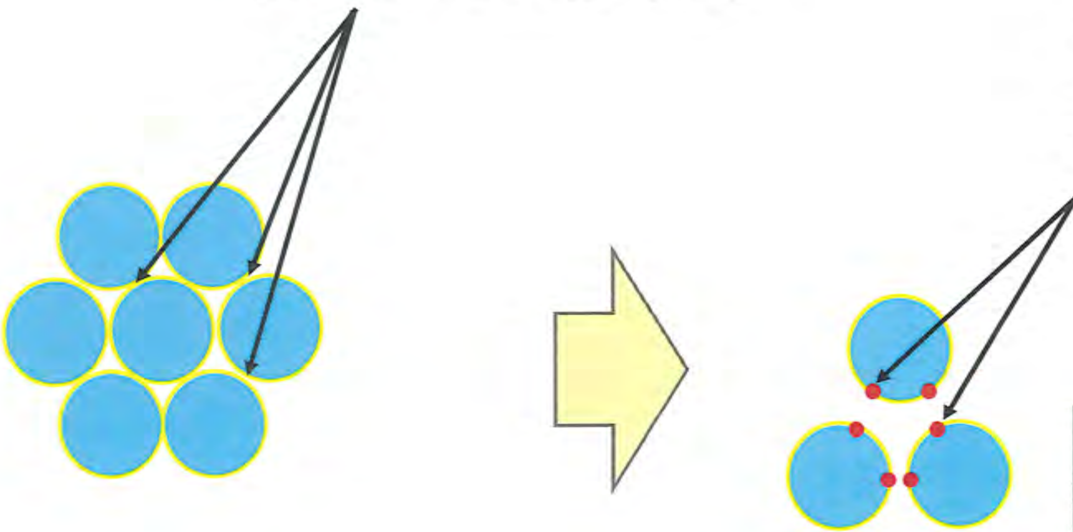
Competitor samples appear not to have the same artefacts – we scanned the filaments extensively





Gynemesh PS filament surface effects – possible causes

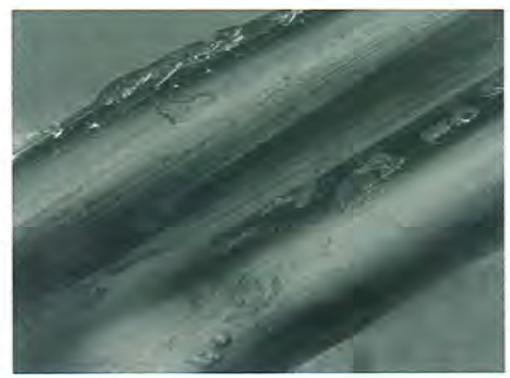
Points of contact along turns of continuous filament once wound up



If the filament has not fully cooled and 'set' prior to winding, it may be 'tacky' in places.

Hence when it is wound up, it will essentially adhere to itself forming 'bridges' between strands

Upon unwinding the bridges snap, material is either removed or deposited at the points of contact.



Some of the artefacts seen may also arise from process variables; e.g. temperature effects at the extrusion die, water content of the polymer and the finish of the tool.

Others may be due to residual processing materials that have not been completely removed through scouring

Polypropylene may have variable properties

- Materials used in mesh production include polyester (PES), polypropylene (PP) and PTFE, as well as resorbable materials
- Materials are a critical component of the mesh and PP has become the preferred material of choice for most manufacturers
- This variable factor was not within the scope of this review, hence we have not evaluated, for example, specifications for raw material PP feedstock in filament extrusion
- However:
  - It is noted that polypropylene has a number of variables; e.g. tacticity - which impacts on degree of crystallinity; and molecular weight distribution
  - There may be other variables; e.g. presence of extrusion processing aids, monomers, dimers, residual catalyst, etc.
  - It is unknown how variations in these material properties might effect properties of extruded filament and ultimately the behaviour of mesh articles produced using it

Isotactic polypropylene

Syndiotactic polypropylene

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Polypropylene can suffer from degradation following implant

- Polypropylene has a long history of use but it is subject to degradation; a process which initiates after a few days post implantation in animal studies[1]
  - This study proposes oxidation as the degradation mechanism, reporting that polypropylene filaments containing an antioxidant were less susceptible to oxidation
  - Oxidation usually occurs at the tertiary repeating position in the polymer, where a free radical is formed that then reacts with oxygen, followed by chain scission to produce aldehydes and carboxylic acids. In external applications, it shows up as a network of fine cracks that become deeper and more severe with time of exposure
  - Degradation of polypropylene has also been reported in the eye, where sutures were used to implant an intraocular lens[2] ; the authors suggest enzymatic degradation
  - Macrophages excrete acidic compounds that can initiate oxidation processes[4]
  - One clinician interviewed proposed that variability in the raw materials, and/or processing thereof, could be affecting the clinical performance and outcomes. He articulated his intention to investigate this hypothesis
  - High resolution images[3] of excised meshes clearly show physical degradation of polypropylene filaments

Tertiary carbon position

1. *Liebert, chartoff, et al J Biomed Mater Res. 1976 Nov;10(6):939-51.*
2. *WL Jongeboed and JFG Worst Documenta opthalmologica; Vol. 64, No1, 143-152*
3. *Images on file, Prof Bernd Klosterhalfen, Technischer Leiter Pathohistologie, Aachen*
4. *Costello CR. Materials characterization of explanted polypropylene hernia meshes. J Biomat Res B Appl Biomater 2007;83:44-9*

Polyester & PTFE are still used for mesh production but cannot be recommended

- Polyester seems essentially redundant as a mesh material, owing to its association with poor clinical outcomes; except in France where reimbursement rules encourage use of polyester
  - In one study, French investigators claim that Polyethylene terephtahlate explants appeared to sustain less degradation in vivo than the PP explants[1]
  - However, it is known that polyester fabrics undergo hydrolytic degradation, accompanied by loss of low weight species and a decrease in weight and burst strength[2]
- PTFE mesh (as opposed to porous film) is available, e.g. Gore® Infinit® mesh; www.goremedical.com
  - Originally, PTFE was available as microporous film, providing lower adhesion owing to its surface properties. PA's analysis of the literature shows that it was highly prone to erosion based failure
  - However, this structure limits both fibroblast and inflammatory cell ingrowth
  - PTFE has a very low surface energy; not conducive to fibroblast attachment
  - Surgical Mesh® also offer a range of PTFE (and other) meshes; www.surgicalmesh.com
- There are also combination products, including collagen coatings and biodegradable materials (e.g. monocryl) to improve handling and encourage cell proliferation

Explanted polyester vascular graft

Gore PTFE mesh©

1. International Urogynecology Journal Volume 21, Number 3, 261-270, Arnaud Clavé, Hannah Yahi, et.al.
2. Microstructural changes in polyester biotextiles during implantation in humans . Martin W. King, Ze Zhang and Robert Guidoin, NC State University, USA.

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Mesh properties are likely to influence propensity for erosion

- There is a huge choice in the weave pattern for the mesh and those on the market attest to the variety of possibilities
- The knitting process produces a mesh with a 'technical front' and 'technical back'; these have different surface characteristics ('roughness') owing to the mesh construction
- Some of the meshes clearly differ in texture on the opposing faces
  - Surgeon's appear unaware of this property
  - It is not known whether the choice of face in contact with the tissue can affect propensity for mesh erosion
- In 2006, a type of surgical mesh used for stress urinary incontinence, known as the ObTape Vaginal Sling, was removed from the market by Mentor Corporation just three years after it was introduced when a large number of women experienced severe problems.
- The Mentor ObTape surgical mesh differed from most other mesh devices, since it contained a "non-woven" design. This blocked oxygen and nutrients, substantially increasing the risk of surgical mesh problems, and some estimates suggested that the complication rate could be as high as 17% to 18%.

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Surgeon experience may be a key factor contributing to erosion

- Several post surgical complications are identified as "erosion" and there seems to be two broad classes: those that appear in the short term (6 – 8 weeks) post surgery and those that may take many months to become symptomatic
  - It is suggested that the former arise as a result of flawed surgical technique. There is general agreement that once implanted, factors such as: folds or creases in the mesh, prominent suture lines, hard or rough edges have a propensity to cause mesh erosion
  - EU working time directive was raised as an issue; resulting in insufficient surgeon training
  - It was suggested that mesh may be being used inappropriately by surgeons with insufficient expertise/training
- Farrel[1] reported that in a group of surgeons asked to identify tissue via handling with forceps:
  - 100% correctly identified vaginal wall
  - 58% correctly identified fascia
  - 67% correctly identified areolar tissue
  - The implication is that what a surgeon believes to be fascia, may in fact be other tissue less suited for permanent repair using mesh
- Highly skilled (i.e. sub-specialist) surgeons use mesh conservatively (particularly in the UK) and avoid use of insertion kits
  - It is possible that the trans-vaginal kits encourage use by less skilled surgeons and there is some evidence that implants inserted with kits suffer a higher rate of erosion than when the mesh is used without an insertion kit

1 Farrel, et.al. Histologic examination of facia used in colporrhaphy. Obstet Gynocol. 200198;794-8

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Type of surgery and indication potentially influences propensity for erosion

- Surgical repairs involving use of mesh include:
  - Sacrocolpopexy
  - Infracococcygeal sacropexy
  - Uterine suspension sling
  - Other techniques
- Suture technique may influence erosion through scarring or suture line separation
  - Mark Slack reported that following review and discussion with cosmetic surgeons, he now uses a two-layer closure technique
- Tension imparted into the mesh before it is fixed may vary widely and could influence erosion
  - "Tension-free" can be a misleading term, particularly if the mesh is being used to suspend or support an organ
- Hematoma formation and depth of implantation are also reported as contributory factors
- Clinicians emphasized the need for more comprehensive pre-clinical and clinical supporting data for mesh products; and cited this as a major hurdle to more widespread use of mesh
  - Products are introduced to the market on the basis of 'substantial equivalence', with insufficient data prior to launch
- Mark Slack suggested
  - A 20 animal pre-clinical study
  - Cadevaric studies
  - 115 patient pilot clinical study, with 12 month follow-up

Patient population potentially influences propensity for erosion

- Multiple factors are said to influence propensity to mesh erosion. The factor raised in interviews by more than one interviewee was the potential for low estrogen to have an effect
  - The difference between pre- and post-menopausal women has not apparently been studied although surgeons noted this was potentially an issue
  - The first line treatment for erosion and post operative care is to use topical estrogen cream (the Sales Representative we interviewed suggested that estrogen replacement therapy should be continued indefinitely)
- There are also a number of patient-centric factors that are known to be associated with mesh erosion, e.g. obesity, age, smoking, co-morbidities, etc.
  - J&J has no control over these factors

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We have analysed J&J's own mesh analysis and attempted to correlate the results with the literature

Material	Manufacturer	Erosion rate		Burst Strength (psi)	Thickness (mils)	Unit Weight (mg/cm²)	Flexural Rigidity (mg cm)		Max Load (lbf)	% Strain	Max Load (lbf)	% Strain	Surface area (in²)	Pore Size (mm)	Porosity (%)	Fiber Diameter (mm)
		abdominal	vaginal				MD	CD	MD	MD	CD	CD				
Polyform	Boston Scientific			10	7.9 (F)	4.0 (F)	289 (F)	130 (F)	21.6 (F)	76.4 (F)	20.6 (F)	109.2 (F)	24	1.5	60.9	0.12
Avaulta	BARD		32.5	102	16.7 (B)	48.4 (B)	601 (B)						15.2-16.8	1.9		0.108 (B)
Apogee system (IntePro)	AMS					5.5 (B)	107 (B)						17.4			0.117(B)
Perigee system (IntePro)	AMS			106	21.9 (B)								21.9	2.4(B)	63.4 (B)	0.116(B)
ULTRAPRO	Ethicon			140	24.3 (F)	5.7 (F)	615 (F)	179 (F)	51.2 (F)	53.4 (F)	10.0 (F)	113.6 (F)		2.5	69.2	0.118
PROLENE soft (PP)	Ethicon			116	18.2 (F)	4.0 (F)	99 (F)	200 (F)	21.1 (F)	76.2 (F)	23.7 (F)	60.9 (F)		2.5	65.6	0.0889
PROLIFT system (Gynemesh)	Ethicon				18.2 (B)								54.1			
Prototype PROLIFT (ULTRAPRO)	Ethicon				25.4 (B)											
SEARAMESH	SERAG Wiessner			126	20.9 (F)	8.3 (F)	671 (F)	312 (F)	32.8 (F)	61.5 (F)	17.1 (F)	110.0 (F)		2.5	60.4	~0.065

F: Flat mesh
B: Body mesh

We cannot draw conclusions as the published literature does not identify the mesh used sufficiently frequently to correlate with the J&J analysis

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Mesh erosion is difficult to model in pre-clinical studies and its difficult to study product improvements clinically

- Product development efforts are complicated by the lack of a definitive animal model for *in-vivo* design validation
  - There are a number of physical mesh properties that may be varied, characterized and measured *in-vitro* but these cannot be easily related to observable outcomes
  - However, we note the general trend over time by all manufacturers to produce meshes with particular general characteristics i.e. larger pore size, monofilament, light weight, etc
- The situation with animal models is confusing; whilst there are claims in the literature for successful animal models as a predictor of product behaviour and performance, these have not been reproduced when adopted by J&J
- The differences in animal anatomy to human anatomy make a model difficult. There are challenges relating to anatomical structures and organization; and histological relevance
- The consensus in J&J is that the animal models are not yet good enough and the organization is endeavouring to develop a new animal model
  - This is challenging; study size is an issue (to detect low failure rates) and there are many influencing factors. The follow up period is also significant
  - Primates perhaps represent the best model, but are very expensive to use in this way and there may be regulatory limitations to consider
  - Sheep are perhaps the next best in terms of vaginal anatomy, but again are costly to utilize

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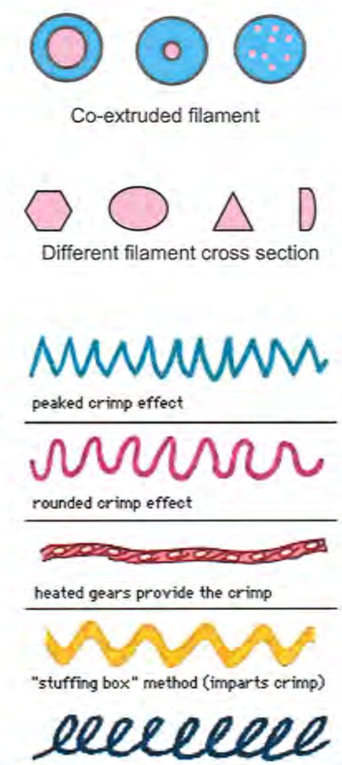
Product development routes and concepts for consideration

- Alternative polymers from which the mesh is made
- Gross mesh properties (pore size, surface area, weight, drape, etc) are defined and achieved through choice of filament diameters and knitting pattern
  - Prof. Klosterhalfen suggested that a light weight product with elasticity in all directions maybe advantageous
- There are also other filament variables that may influence mesh properties, for example
  - Filament cross section shape and size and combinations thereof; essentially limitless
  - Longitudinal filament crimping or coiling may be used to impart stretch/elasticity to the mesh
- Alternative fabric production processes
  - 3-d knitting
  - Continuous filament needle punching; non woven



Product development routes and concepts for consideration

- One theory is that the better the bio-stability of the material the lower to potential for mesh erosion[1]
  - Pronova was suggested as a more stable material with the elastic properties required for pelvic floor repair mesh[1]
- Polymer additives
  - Antioxidants to reduce oxidative degradation and improve material stability
- Micro coatings to produce an inert surface, e.g.
  - Titanium nitride (TiN) used on orthopaedic implants
  - Liquid glass, SiO_2
- Coatings or additives to reduce infection and biofilm formation
  - Antimicrobials, antibiotics
  - Silver, nanocrystalline
- Coatings to support assimilation into the host
  - Oestrogen, tissue growth factors
  - Bioadhesives, fibrin glue, fibronectin, collagen
- Post production forming of knitted mesh
  - 3-d shapes; e.g. thermoforming of knitted mesh, personalized shapes?
  - Seamless knitted tubes, these could be radially elastic (like tubular bandages)

1 Professor Klosterhalfen observations and theory

ETH.MESH.02589078

Suggested further work

- Investigate potential material variability
- Investigate all stages of processing and impact on physical attributes of filament and mesh
- Consider surgeon training – sponsorship, etc
- Investigate methods to limit mesh degradation - coatings, additives, etc.
- Evaluate mesh design options
- Review and consider product concepts